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Relationship between first-trimester vitamin D levels and gestational diabetes mellitus

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Abstract
Aim: In this study, we aimed to examine the association between first-trimester maternal 25(OH)D levels and GDM status.
Material and Methods: We retrospectively reviewed the records of pregnant women admitted to the antenatal outpatient clinic during the first trimester (6–13 weeks) and subsequent oral glucose tolerance testing (OGTT) between September 2013 to June 2014. GDM was diagnosed according to the International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria.
Results: A total of 189 pregnant women, of whom 14.8% (28/189) were GDM. It was found that no subject had sufficient levels of 25(OH)D and the majority of patients (69.8% (132/189)) had severe vitamin D deficiency. Binary logistic regression analysis revealed that 25(OH)D levels at 6-14 weeks of gestation, insulin levels had no significant impact on GDM.
Discussion: In the first trimester of pregnancy, 25(OH)D levels were not associated with GDM. Additionally, there was a high frequency of vitamin D deficiency among pregnant women.

Keywords
GDM, Gestational Diabetes Mellitus, Vitamin D Deficiency

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Introduction

Gestational diabetes mellitus (GDM) is defined as any degree of glucose elevation during pregnancy [1], with a prevalence ranging from 5% to 25% of all pregnancies [2]. GDM is the most common metabolic disorder diagnosed during pregnancy [3], which leads to short and long-term adverse health consequences for both mothers and their children [4]. There are expanding numbers of studies focusing on the possible causes of GDM, such as interest in vitamin D deficiency, as a possible cause.

Vitamin D plays an important role in pregnancy due to its impact on bone and muscle health [5], regulation of calcium and phosphorus metabolism, glucose balance, placental functions, embryogenesis [6], and maturation of the respiratory system [7]. Given the increasing prevalence of vitamin D deficiency among pregnant [8] and childbearing-aged women in developing countries [9], it is of great importance to evaluate the effect of maternal 25(OH)D level on GDM.

Research on 25(OH)D and GDM has driven for over a decade yielding different results. Several studies have shown a significant relationship between 25(OH)D levels and the risk of GDM [10], whereas others could not demonstrate any significant results on this association [11]. The data regarding the effect of the 25(OH)D level on GDM development and related mechanisms are inconsistent. Thus, in this study, we aimed to examine the relationship between maternal 25(OH)D levels in the early trimester and GDM status.

Material and Methods

We retrospectively searched the results of serum 25(OH)D tests of pregnant women who attended the outpatient clinic of Obstetrics and Gynecology at Zeynep Kamil Women and Children's Disease Training and Research Hospital for routine antenatal care during the first trimester (6–13 weeks) and subsequent oral glucose tolerance testing (OGTT) between September 2013 to June 2014. Our hospital is a tertiary referral health facility that provides comprehensive level care for mothers, newborns, and children.

The data were extracted from the hospital's electronic database after the approval by the Research Ethics Committee (Approval number: 25, 13.01.2015). Database management complies with legislation on privacy and this research is under the ethical principles of the Declaration of Helsinki. Informed consent was waived due to the retrospective study design by the same ethics committee that approved this study.

We performed a sample size calculation based on a previously published study [12], a sample size of 20 per group was needed, with a 95% confidence level and a margin error of 0.05

Abstracted data included maternal age, body mass index (BMI), obstetric history, gestational age at admission, first-trimester plasma fasting glucose, 25(OH)D, and insulin levels, results of 75 g OGTT at 24-28 weeks of pregnancy. Patients aged 18 and above who had a singleton pregnancy, had no history of chronic diseases, and complete data were included in the study. Patients who had a history of GDM, type 1 and 2 diabetes, pre-eclampsia, thyroid and parathyroid disease, renal failure or other diseases that influence glucose metabolism, multiple pregnancies, consumption of drugs that interact with glucose, calcium, and vitamin D metabolism, except for vitamin D supplements prescribed during pregnancy, and those who had incomplete data were excluded from the study.

The electrochemiluminescent method (Roche diagnostics GmBH Mannheim, Germany) was used for measuring 25(OH)D3 levels with a COBAS e411 instrument. The analytical sensitivity of the assay was 3ng/ml; the total coefficient of variation percentage (CV%) at 15ng/ml was 5.1%; the total CV at 28 ng/ml was 3.1%. The insulin level was measured using the one-step immuno-enzymatic sandwich method. Glucose levels were measured using the enzymatic UV hexokinase method in the AU5800 auto-analyzer (Beckman Coulter, Brea, CA, USA). All analyses were performed in the biochemistry laboratory of the same hospital.

According to the Endocrine Society Clinical Practice Guidelines, vitamin D sufficiency was defined as >30 ng/mL, insufficiency as 20–30 ng/mL, deficiency as 10-19 ng/mL, and severe deficiency as <10 ng/mL [13]. GDM was defined according to the International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria [14]. Gestational age at delivery was calculated based on the first date of the last menstrual period. The parity of women was defined as the total number of children ever born. Body mass index (BMI) was calculated for mothers in the first trimester as weight in kilograms divided by the square of height in meters (kg/m2) and evaluated based on the World Health Organization classification [15].

Statistical Analysis

Analyzes were carried out using the Statistical Package for the Social Science (IBM SPSS, Version 25.0. Armonk, NY: IBM Corp.) for Windows software. Data were expressed as frequency (n) and percentage (%) for qualitative variables and arithmetic mean and standard deviation values (Mean+SD) for quantitative variables. The x^2 or Fisher's exact tests were used for categorical variables and the independent-sample t-test was used for continuous variables. The one-way analysis of variance (ANOVA) test followed by the Tukey post-hoc test was performed for multiple comparisons. The type I error rate was set at 0.05. A p-value <0.05 was considered statistically significant.

Ethical Approval

Ethics Committee approval for the study was obtained.

Results

The subjects included in this analysis were those who had 25(OH)D within the first trimester (n=189) and were screened for OGTT at 24-28 weeks of pregnancy. The baseline characteristics of patients diagnosed with GDM and those with normal plasma glucose are summarized in Table 1. Among the study patients, the number of pregnant women with GDM accounted for 14.8% (28/189). The median age of patients with and without GDM was 30 (range: 23-43) and 28 (range: 18-40) years, respectively. There was no significant difference between the two groups with respect to maternal age (p=0,090).

At 6-14 weeks of pregnancy, the insulin levels were higher in the GDM group compared to the non-GDM group (10.9 (range: 2-59.3) vs 7.4 (range: 2.1-73.4)). The insulin levels were significantly different between the two groups (p=0,005).

The subjects were classified according to the cut-offs of

Table 1. Characteristics of mothers with GDM vs. control mothers.

Variables		Healthy	GDM	p
Maternal age (years)		28 (18-40)	30 (23-43)	0.090
Gestational age (weeks)		9 (6-14)	10,5 (6-14)	0.121
BMI (kg/m2)	18.5-24.9	74 (93.7)	5 (6.3)	0.011*
	25.0-29.9	49 (84.5)	9 (15.5)	
	30.0-34.9	23 (69.7)	10 (30.3)	
	35.0-39.9	7 (87.5)	1 (12.5)	
Gravity	0	12 (75)	4 (25)	0.119
	1	40 (90.9)	4 (9.1)	
	2	33 (97.1)	1 (2.9)	
	3+	40 (90.9)	4 (9.1)	
Fasting insulin (µIU/mL)		7.4 (2.1-73.4)	10.9 (2-59.3)	0.005*
25(OH)D status	Severe deficiency (<10 ng/mL)	115 (87.1)	17 (12.9)	0.049*
	Deficiency (10-20 ng/mL)	33 (75)	11 (25)	
	Insufficiency (20-30 ng/mL)	13 (100)	0 (0)	

Abbreviations: 25(OH)D, 25-hydoxyvitamin D; GDM: Gestational diabetes mellitus, BMI: Body mass index

Table 2. Binary logistic regression analysis of factors affecting gestational diabetes mellitus (GDM).

		B	SE	Wald	p-value	OR (95% CI)
BMI (kg/m2)	18.5-24.9			5,672	0,129	
	25.0-29.9	0,941	0,603	2,431	0,119	2,561 (0,785-8,356)
	30.0-34.9	1,51	0,636	5,627	0,018*	4,526 (1,3-15,756)
	35.0-39.9	0,767	1,19	0,415	0,519	2,153 (0,209-22,179)
25(OH)D status	Severe deficiency (<10 ng/mL)			2,342	0,310	
	Deficiency (10-20 ng/mL)	0,752	0,491	2,342	0,126	2,121 (0,81-5,556)
	Insufficiency (20-30 ng/mL)	-18,838	12531,6	0	0,999	0 (0-.)
Insulin		0,007	0,022	0,094	0,759	1,007 (0,964-1,051)
Constant		-7,994	4177,2	0	0,998	0

Abbreviations: 25(OH)D, 25-hydoxyvitamin D; OR, odds ratio; CI, confidence interval, BMI: Body mass index

25(OH)D levels. It was found that no subject had sufficient levels of 25(OH)D. The majority of patients had severe vitamin D deficiency. The severe 25(OH)D deficiency at 6-14 weeks of gestation was 12.9% in women with GDM and 87.1% in non-GDM controls. Additionally, 25(OH)D deficiency was found higher in non-GDM women compared to those in GDM women; there was a statistically significant difference observed between the two groups (p=0,049).

Binary logistic regression analysis revealed that 25(OH)D levels at 6-14 weeks of gestation, insulin levels had no significant impact on GDM. Obesity (BMI values: 30-34.9) was statistically significant with GDM (Table 2).

Discussion

This study revealed that there were no significant differences in first trimester 25(OH)D levels between GDM and non-GDM women screened at 24-28 weeks of pregnancy. Additionally, there was a high frequency of vitamin D deficiency among pregnant women. GDM development was not associated with the first trimester maternal 25(OH)D and insulin levels. Notably, none of the pregnant women had sufficient 25(OH)D levels, and all women diagnosed with GDM had 25(OH)D concentrations <20 ng/mL.

The relationship between 25(OH)D deficiency and GDM remains unclear. Our study findings are in line with the study conducted by Bal et al. who also investigated maternal serum 25(OH)D levels in the first trimester in women with and without GDM, and they failed to find an association with 25(OH)D levels compared to those in women at low risk for GDM [16]. Tkachuk et al. investigated the link between maternal serum 25(OH)D levels in the first and second trimesters of pregnancy and GDM [17]. Similar to our findings, they concluded that there was no association between GDM risk and vitamin D levels measured in the first trimesters of pregnancy. A systematic review and meta-analysis study conducted by Martínez-Domínguez et al. reported that they also failed to find an association between the first-trimester maternal serum 25(OH) D levels and the development of GDM [18]. Likewise, Hauta-Alus et al. reported that maternal 25(OH)D levels were similar in women with and without GDM in a mostly vitamin D sufficient population [19]. A cross-sectional study from Turkey found no association between 25(OH)D deficiency and the risk of GDM, which is compatible with our study findings [20].

On the other hand, some studies report a meaningful association between vitamin D deficiency and risk of GDM. Xue et al. have recently examined the complex issue of the relationship between 25(OH) levels and the development of GDM. They concluded that low 25(OH)D levels in the first trimester were associated with an increased risk of GDM [21]. Similarly, a recent study indicated that low 25(OH)D levels were associated with an increased odds of GDM [22]. Another study found that women with low 25(OH)D levels had a higher risk of developing GDM [23]. However, it remains unclear whether vitamin D deficiency contributes to maternal risk of developing GDM. These conflicting results might be related to methodological issues, the techniques used to measure vitamin D, the definition of vitamin D deficiency, the trimester at sampling, and the diagnostic criteria for GDM. Additionally, some factors, such as maternal age, weight gain, lifestyle, family history of diabetes, exposure to sunlight, consumption of prenatal multivitamin supplements, smoking, alcohol consumption, race/ethnicity might have contributed to contradictory findings between studies. It is plausible that several limitations might have influenced the results obtained. Unfortunately, due to the retrospective nature of the study, we were unable to obtain relevant data on the patients' socioeconomic, demographic characteristics, clinical features, eating habits and dietary intake, and sunlight exposure. Inevitably, another possible source of error is a single-center design with a small sample size, which makes the results less generalizable, and this should be kept in mind in the interpretation of the results. Notwithstanding the relatively limited sample, our research provides valuable insights into the growing body of literature on the association between maternal 25(OH)D level and the development of GDM. We believe that

our findings may still be useful as baseline information for subsequent epidemiological studies.

Conclusion

The present study indicated that in the first trimester, 25(OH) D levels were not associated with GDM. Further well-designed, large and prospective cohort studies are needed to develop a deeper understanding of the complex interaction between 25(OH)D status and the development of GDM.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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